REMARKS

I. Status of the Claims

Claims 63-104 and 108-112 are pending and under examination. Claims 1-62 and 105-107 were canceled previously, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications to the canceled subject matter.

The Office highlighted several grammatical and typographical mistakes in the pending claim set. See "Claim Objections" at page 3. Applicants believe the presently-amended claim set addresses each of those points and therefore believe they have overcome those objections.

II. New Matter Objection under 35 U.S.C. § 132(a)

The Office maintains that Applicants' preliminary amendment of June 7, 2004, introduces new matter under Section 132(a) because the subject matter therein ("Examples 17-31, everything relating to Figures 12-20, [and] every reference to monomer and exogenous factors") is "not supported by the original disclosure." Office action at page 2.

Applicants respectfully point out that the preliminary amendment in question did not introduce new matter because it was filed concurrently with a new substitute specification on November 28, 2003. This comports with Applicants' inventor declaration, also concurrently filed at that time, which requested a priority date of November 28, 2003, for the *completed* application, as opposed to the earlier date of November 26th, when the specification text was deposited with the PTO. In other words, the subject matter of the preliminary amendment is not "new" with respect to documentation on file by November 28th. Accordingly, Applicants have not canceled the matter which the Office purports to be "new."

On an analogous note, Applicants shall soon submit certified English translations of the Japanese priority documents in order to formerly obtain "the benefit of [that] foreign priority under 35 U.S.C. § 120 or 119(a)-(d)" as the Office requires (page 6 of the action).

III. Rejections under 35 U.S.C. 112, second paragraph

Claims 63, 64, 69, 74, 79, 84, 89, 94, 100, 104, and 108-112 and their dependent claims are rejected, at pages 3-5 of the action, as allegedly indefinite because the Office believes the following recited phrases are unclear. Applicants thank Examiner Kaufman for

her detailed and thorough review of the language of the claims and her suggestions for revising the relevant recitations. Applicants believe the claims as presented in the current listing of the claims addresses each of Examiner Kaufman's indefiniteness rejections:

(i) "monomer independently of exogenous factors" 63, 64, 69, 74, 79, 84, 89, 94, and 100. Applicants intended this phrase to convey the novel fact that the claimed antibody (or a fragment thereof) by itself can bind to TRAIL-R2 and thereby induce apoptosis. That is, the present invention eliminates the prior art's necessity for additional components or antibody complex formation which was meant to be explicitly conveyed by the denoted phrase. Applicants illuminate this intent by clarifying that the monomeric antibody (or a fragment thereof) exerts its apoptosis-inducing activity as "a single substance without forming a polymer." Literal support for this amendment is found at paragraph 77 of the published U.S. application, U.S. 2005/0249729. Accordingly, Applicants believe it is now clearer that the monomer antibody works "independently" of any other exogenous factors.

(ii) "as a monomer" recited in claims 63, 64, 69, 74, 79, 84, 89, 94, 100, and 108. Applicants believe the present amendments and the rationale presented in subsection (i) above obviate this rejection;

(iii) "exogenous factor" recited in claims 63, 64, 69, 74, 79, 84, 89, 94, and 100. Applicants believe the present amendments and the rationale presented in subsection (i) above obviate this rejection;

(iv) "TRAIL-R" recited in claims 63, 64, 69, 74, 79, 84, 89, 94, 100, and 108. Applicants have amended the claims to recite TRAIL-R**2**;

(v) "reducibility of the mitochondria" recited in claims 63, 64, 69, 74, 79, and 109-112. Applicants relate that apoptosis necessarily causes destruction of mitochondria. Hence, the "reducibility of the mitochondria" is useful indicator of the progression of apoptosis. Applicants direct the Examiner to Example 29, which relates the reducibility/destruction of mitochondria as a suitable apoptosis assay.

(vi) "the [or said] antibody bound to TRAIL-R" recited in claims 84, 94, 100, and 101. Applicants have amended the claims to recite TRAIL-R**2**;

(vii) "80% or less" recited in claims 84, 89, and 94. Applicants thank Examiner Kaufman for her suggestion to move the "80%" qualification to "immediately follow 'survival rate of'" in the denoted claims. Applicants have implemented that suggestion;

(viii) "wherein 'a' represents the measured value of a well tested" recited in claims 64, 69, 74, 79, and 109-112. Applicants have amended the claims to make clearer that it is the absorbance of a well containing carcinoma cells whose value is being measured;

(ix) "the antigenicity" recited in claim 108. Applicants have deleted the phase;

(x) "or the like" recited in claim 104. Applicants have deleted the phase.

IV. Griffith does not teach a monomeric agent that, by itself, induces apoptosis via binding to TRAIL-R2 and therefore does not anticipate the claimed invention

Claims 63-104 and 108 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Griffith *et al.*, *J. Immunol.* 162:2597, 1999 ("Griffith"). According to the Office, Griffith raised several monoclonal antibodies to various TRAIL receptors and tested them for apoptosis-inducing activity. Office action at page 7.

Applicants respectfully assert that Griffith does not teach a "monoclonal antibody or a functional fragment thereof, which is a single substance without forming a polymer, binding to TRAIL-R2 and induces apoptosis in carcinoma cells expressing TRAIL-R2, independently of exogenous factors other than the antibody and the functional fragment thereof." Indeed, Griffith teaches away from the present invention because Griffith concludes that "TRAIL-R1 or –R2 ligation does not always lead to death." See the sentence beginning at the bottom of the left-hand column on page 2604. That is, apoptosis in Griffith's hands requires ***multiple*** factors: "[I]t seems likely that multiple factors function together to provide resistance against the cytotoxic effects of TRAIL." *Id.* at right-hand column. Furthermore, Griffith informs that "many questions still remain unanswered." *Id.*

Clearly, Griffith does not teach a monomeric agent that, by itself, induces apoptosis via binding to TRAIL-R2. Accordingly, Griffith does not anticipate the claimed invention and therefore Applicants respectfully request withdrawal of this rejection.

V. Neither U.S. Patent No. 6,342,369 nor U.S. 2003/0190687 teaches production of monoclonal antibodies that induce the death of cells that express TRAIL-R2, without polymerization of those monomeric components, and Applicants are generating corroborative data in this regard

Applicants are making a good faith attempt to meet the Office's threshold prerequisite that applicants, in general, could be "required to prove that prior art products do not necessarily or inherently possess characteristics" of, in this case, the claimed monoclonal antibodies. Office action at page 9. Applicants therefore are conducting

experiments to compare the prior art's antibodies against those presently claimed to provide evidence that, actually, the prior art compounds do not function like Applicants' "single substance." Due to the nature of antibody preparation and comparative studies, Applicants are not yet in a position, at the time of writing, to communicate the results of that work. Accordingly, for now, Applicants note the following remarks concerning U.S. Patent No. 6,342,369 and U.S. 2003/0190687:

(i) U.S. Patent No. 6,342,369 (antibody 16E2)

Claims 63-104 and 108 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by United States Patent 6,342,369 (issued January 29, 2002). According to the Office, the '369 patent described methods that "did not use the same assay used to characterize the claimed antibody . . . but it appears absent evidence to the contrary that antibody 16E2 has the required functional properties required by the instant claims." Office action at page 8.

In fact, the '369 patent does *not* describe an antibody that is "a single substance" that binds to TRAIL-R2 receptors that are expressed in carcinoma cells and thereby induces death of those cancerous cells. Applicants presently are conducting experiments to provide "evidence to the contrary" that, actually, antibody 16E2 is functionally similar to the claimed monoclonal antibody. At the time of this filing, however, Applicants have not completed their antibody studies, but shall consider submitting an appropriate declaration to the Office explaining the outcome of those experiments and highlighting the distinguishing properties between the claimed antibody and 16E2.

(ii) U.S. 2003/0190687 (antibody TRA-8)

Claims 63-104 and 108 are rejected under 35 U.S.C. § 102(e) or 102(a) as allegedly anticipated by United States application publication U.S. 2003/0190687 (published October 9, 2003; priority to May 2, 2001). The antibody there, TRA-8, "appears to have all the properties" of the claimed antibody.

Applicants assert however that their preliminary experiments indicate that TRA-8 cannot induce apoptosis "as a single substance without forming a polymer." Applicants assert that TRA-8 only can induce apoptosis when it forms a polymer by aggregation. At the time of writing, Applicants have not completed this comparative antibody study, but shall consider filing a declaration soon after this paper's submission date to corroborate their

assertions and to provide the "evidence to the contrary" concerning the TRA-8 antibody of US 2003/0190687.

CONCLUSION

Applicants invite Examiner Kaufman to contact the undersigned by telephone if that would expedite prosecution.

Respectfully submitted,

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